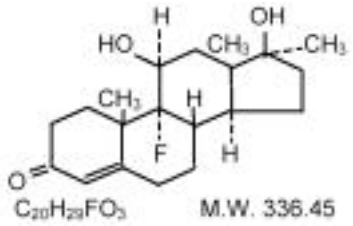
ANDROXY - fluoxymesterone tablet
UPSHER-SMITH LABORATORIES, INC.

CIII
REV. 5-04
15021-09
ANDROXY™ (Fluoxymesterone Tablets, USP)
Rx only

DESCRIPTION

ANDROXY™ (Fluoxymesterone Tablets, USP) contains fluoxymesterone, a synthetic androgen. The androgens are steroids that develop and maintain primary and secondary male sex characteristics. Androgens are derivatives of cyclopentano-perhydrophenanthrene. Endogenous androgens are C-19 steroids with a side chain at C-17, and with two angular methyl groups. Testosterone is the primary endogenous androgen. Fluoxymesterone is a synthetic derivative of testosterone.
In their active form, all drugs in the class have a 17-beta-hydroxy group. 17-alpha-alkylation and halogenation at position 9 (fluoxymesterone) increase the pharmacologic activity per unit weight compared to testosterone when given orally. Fluoxymesterone is a white or practically white odorless, crystalline powder, melting at about 240°C with some decomposition. It is practically insoluble in water, sparingly soluble in alcohol and slightly soluble in chloroform. Chemically fluoxymesterone is designated 9-fluoro-11β, 17β-dihydroxy-17-methylandrost-4-en-3-one. Structurally it may be represented as follows:



$C_{20}H_{29}FO_3$ M.W. 336.45

ANDROXY™ (Fluoxymesteron Tablets, USP) for oral administration contains 10 mg of fluoxymesterone USP.
Inactive Ingredients: croscarmellose sodium, D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, anhydrous lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include growth and maturation of prostate, seminal vesicles, penis, and scrotum; development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.
Androgens also cause retention of nitrogen, sodium, potassium, and phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.
Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth which is brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.
During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).
There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

Pharmacokinetics

Testosterone given orally is metabolized by the gut, and 44 percent is cleared by the liver in the first pass. Oral doses as high as 400 mg per day are needed to achieve clinically effective blood levels for full replacement therapy. The 17-alpha-alkylated derivatives (fluoxymesterone and methyltestosterone) are less extensively metabolized by the liver and have longer half lives. They are more suitable for oral administration than testosterone.
Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin, and about two percent is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.
About 90 percent of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about six percent of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs

primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways. There are considerable variations of the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. The half-life of fluoxymesterone is reported to be 10 hours.
In responsive tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

Males
ANDROXY™ Tablets are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.
Primary hypogonadism (congenital or acquired)—Testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy.

Hypogonadotropic hypogonadism (congenital or acquired)—Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. (Appropriate adrenal cortical and thyroid hormone replacement therapy are still necessary, however, and are actually of primary importance.)

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

Delayed puberty—ANDROXY™ (Fluoxymesterone Tablets, USP) may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers (see WARNINGS).

Females
Metastatic mammary cancer—ANDROXY™ (Fluoxymesterone Tablets, USP) may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or antiestrogen therapy. This treatment has been used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field.

CONTRAINDICATIONS
Androgens are contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate and in women who are or may become pregnant. When administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. This virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking androgens, she should be apprised of the potential hazard to the fetus.

WARNINGS
This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.
In patients with breast cancer and in immobilized patients, androgen therapy may cause hypercalcemia by stimulating osteolysis. In patients with cancer, hypercalcemia may indicate progression of bony metastasis. If hypercalcemia occurs, the drug should be discontinued and appropriate measures instituted.
Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma (see PRECAUTIONS, Carcinogenesis). Peliosis hepatis can be a life-threatening or fatal complication.
Cholestatic hepatitis and jaundice occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, the androgen should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.
Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Due to sodium and water retention, edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required. If the administration of fluoxymesterone is restarted, a lower dosage should be used.
Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.
Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every six months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.

PRECAUTIONS

General
Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Such virilization is usual following androgen use at high doses and is not prevented by concomitant use of estrogens. A decision may be made by the patient and the physician that some virilization will be tolerated during treatment for breast carcinoma.
Because androgens may alter serum cholesterol concentration, caution should be used when administering these drugs to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly. A causal relationship between myocardial infarction and hypercholesterolemia has not been established.

Information for Patients
Male adolescent patients receiving androgens for delayed puberty should have bone development checked every six months.
The physician should instruct patients to report any of the following side effects of androgens:
Adult or adolescent males—too frequent or persistent erections of the penis.
Women—hoarseness, acne, changes in menstrual periods, or more facial hair.
All patients—Any nausea, vomiting, changes in skin color, or ankle swelling.

Laboratory Tests
Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of androgen therapy (see WARNINGS).
Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.
Periodic (every six months) X-ray examinations of bone age should be made during treatment of prepubertal males to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.
Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

Drug Interactions
When administered concurrently, the following drugs may interact with androgens:
Anticoagulants, oral—C-17 substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirement. Patients receiving oral anticoagulant therapy require close monitoring especially when androgens are started or stopped.

Antidiabetic drugs and insulin—In diabetic patients, the metabolic effects of androgens may decrease blood glucose and insulin requirements.

ACTH and corticosteroids—Enhanced tendency toward edema. Use caution when giving these drugs together, especially in patients with hepatic or cardiac disease.

Oxyphenbutazone—May result in elevated serum levels of oxyphenbutazone.

Drug/Laboratory Test Interactions
Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis
Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically-induced carcinomas of the liver in rats.
There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy—Teratogenic Effects
Category X (see CONTRAINDICATIONS)

Nursing Mothers
It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every six months by an X-ray of the hand and wrist (see INDICATIONS AND USAGE, and WARNINGS).

ADVERSE REACTIONS
Endocrine and Urogenital, *Female*—The most common side effects of androgen therapy are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administered to a pregnant woman, androgens cause virilization of external genitalia of the female fetus.
Male—Gynecomastia, and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages (see CLINICAL PHARMACOLOGY).
Skin and Appendages—Hirsutism, male pattern baldness, and acne.
Fluid and Electrolyte Disturbances—Retention of sodium, chloride, water, potassium, calcium (see WARNINGS), and inorganic phosphates.
Gastrointestinal—Nausea, cholestatic jaundice, alterations in liver function tests; rarely, hepatocellular neoplasms, peliosis hepatis, hepatic coma, and death. (See WARNINGS.)
Hematologic—Suppression of clotting factors II, V, VII, and X; bleeding in patients on concomitant anticoagulant therapy; and polycythemia.
Nervous System—Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.
Metabolic—Increased serum cholesterol.
Miscellaneous—Hypersensitivity; rarely, anaphylactoid reactions.

DRUG ABUSE AND DEPENDENCE
ANDROXY™ Tablets are classified as a Schedule III controlled substance under the Anabolic Steroids Control Act of 1990.

OVERDOSAGE
There have been no reports of acute overdosage with androgens.

DOSAGE AND ADMINISTRATION
ANDROXY™ (Fluoxymesterone Tablets, USP), for oral administration, may be given as a single daily dose or in divided doses. Dosage and duration of therapy will depend on age, sex, diagnosis, patient's response to treatment, and appearance of adverse effects. The following recommendations will serve as a guide to therapy with ANDROXY™ Tablets.
In males with delayed puberty: Various dosage regimens have been used; some call for lower dosages initially with gradual increases as puberty progresses, with or without a decrease to maintenance levels. Other regimens call for higher dosage to induce pubertal changes and lower dosage for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose. Dosage is within the range of 2.5 to 20 mg daily, although generally in the lower range of 2.5 to 10 mg daily, and for a limited duration, for example 4 to 6 months. X-rays should be taken at appropriate intervals to determine the amount of bone maturation and skeletal development (see INDICATIONS AND USAGE, and WARNINGS).
Male hypoganadism: As replacement therapy, i.e., for eunuchism, a daily dose of 5 to 20 mg is suggested. It is usually preferable to start therapy at a higher level within the range (e.g., 10 mg), with subsequent adjustment as required.
Palliation of inoperable mammary cancer in women: A daily dose of 10 to 40 mg, given in divided doses, is recommended. To determine if there will be an objective response, treatment should be continued for three months or more. Patients must be followed closely because androgen therapy occasionally appears to accelerate the disease. Thus, many experts prefer to use a shorter acting androgen preparation, such as **ANDROXY™** Tablets, rather than those with prolonged activity, particularly during the early stages of androgen therapy.
In palliation of advanced mammary carcinoma: Hormone therapy is adjunctive to and not a replacement for conventional therapy. Duration of therapy will depend on the response of the condition and the appearance of adverse reactions.

HOW SUPPLIED

ANDROXY™ (Fluoxymesterone Tablets, USP) 10 mg are round, green, scored compressed tablets debossed with 832 and 86 and are available in bottles of 100.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15 - 30°C (59 - 86°F).

Keep out of reach of children.

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Manufactured by:

UPSHER-SMITH LABORATORIES, INC.

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